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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,623	06/20/2003	Uri H. Saragovi	351325-0102 OGIL-002 US	7195

48329 7590 11/12/2008

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
11/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,623	SARAGOVI ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29,31-35 and 39* is/are pending in the application.

4a) Of the above claim(s) *1-29 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/17/2008 has been entered.

Claims 1-29, 31-35 and 39 are pending.

Claims 1-29, 31-34 are withdrawn from consideration as being drawn to non-elected species.

Claims 35 and 39 are currently under consideration.

Response to Amendment

The Declaration under 37 CFR 1.132 filed on 9/17/2008 by Uri Saragovi is insufficient to overcome the rejection of claims 35 and 39 under 35 U.S.C. 103(a) as being unpatentable over Saragovi et al. (WO 97/21732, 1997, IDS) in view of Webb et al. (US 6,652,864, filed on 12/21/19980) and Shin et al. (Cancer Immunol. Immunother. 1994; 38: 92-98) as set forth in the last Office action because: the Declaration appears to set forth the surprising discovery of the mechanism of action of immunoconjugates of the present invention, e.g., upregulation of the p-glycoprotein pump or by-passing the p-glycoprotein pump in tumor cells. However, the courts have held that the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Additionally, other than discovering the mechanism of action of the immunoconjugate, the Declaration does not appear to teach what the differences are between the presently claimed method and the method taught in the prior art. For example, the Examiner recognizes that Saragovi et al. teach a method of treating a neoplastic tumor which expresses TrKA receptors such as monoclonal antibody 5C3 in a patient comprising administering an effective amount of an antibody or an antibody-cytotoxic agent immunoconjugate. As such, Saragovi et al. teach administering a monoclonal antibody-cytotoxic conjugate to the same patient population, wherein the antibody is an antibody encompassed by the presently claimed invention. Saragovi et al. do not teach that the

conjugate further comprises a cleavable linker and the cytotoxic agent is doxorubicin. However, as taught by Webb et al., immunoconjugates comprising the monoclonal antibody 5C3 linked to a compound through a cleavable linker are well known in the art; and further, it is well known within the art, as taught by Shih et al., that the non-selectivity of conventional chemotherapeutics such as doxorubicin are overcome by linking the chemotherapeutic agent to a antibody. Thus, one would have a reasonable expectation of success that by modifying the coupled antibody as taught by Saragovi et al. to include doxorubicin as the cytotoxic moiety in view of the teachings of Shih et al., one would achieve a method of reducing the major limitation of non-selectivity of doxorubicin treatment. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saragovi et al. (WO 97/21732, 1997, IDS, of record) as evidenced by Bates et al. (American Journal of Pathology 1991; 139, 305-315) in view of Webb et al. (US 6,652,864, filed on 12/21/19980, of record) and Shin et al. (Cancer Immunol. Immunother. 1994; 38: 92-98, of record) .

Saragovi et al. teach a method of treating a neoplastic tumor which expresses TrKA receptors in a patient comprising administering an effective amount of an antibody or functional fragment thereof (page 4, lines 8-14). With regards to the antibody, the WO document teaches that the antibody includes, but is not limited to, monoclonal antibody 5C3 (page 7, lines 6+). With

regards to the neoplastic tumor which express TrKA receptors, the WO document teaches that the tumors include, but are not limited to, neuroblastoma (page 24, Table 6). Moreover, the WO document teaches that the method of treating a tumor further comprises coupling a cytotoxic agent to the antibody and administering to said patient the coupled antibody (page 5, lines 8-14). Thus, while Saragovi et al. does not explicitly teach that the patient having a neuroblastoma includes drug resistant tumor cells, the claimed limitation does not appear to result in a manipulative difference because as evidenced by Bates et al., p-glycoprotein is expressed at different levels in neuroblastoma's. Thus, the patient populations appear to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the patient population of the prior art does not possess the same material, structural and functional characteristics of the claimed patient population. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed patient population is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Saragovi et al. do not explicitly teach that the coupled antibody has the formula W-Z-X, wherein X is a chemotherapeutic agent selected from the group consisting of doxorubicin and paclitaxel, W is the monoclonal antibody, 5C3, and z is a breakable linker which covalently links W and X.

Webb et al. teach a compound having the formula B-L-M, wherein B is a binding agent capable of selectively binding to a nerve cell surface receptor, M is a moiety and L is a linker which couples L to M (column 2, lines 3-14). In particular, the patent teaches that the binding agents are antibodies including, but not limited to, monoclonal antibodies 5C3 and anti-human p75 monoclonal antibody MC192 (column 2, lines 56-60). Moreover, the patent teaches that linker is a cleavable linker which enables the moiety M linked to the binding agent B to be released from the compound once absorbed by the nerve cell (column 3, liens 16-20).

Shih et al. teach that the major limitation of conventional cancer chemotherapy is the non-selectivity of this treatment, wherein the maximum tolerated dose that a patient can receive is often lower than is necessary for tumor destruction (page 92, 2nd column, 1st paragraph). As such, Shin et al. teach a doxorubicin immunoconjugate, e.g., doxorubicin conjugated to an anti-CEA antibody,

which exhibited substantially increased tumorcidal effects over those of the unconjugated doxorubicin in the tumor system that has been resistant to most of the available chemotherapeutic agents, and revealed minimal host toxicity when compared to an equivalent dose of the free drug, e.g., unconjugated doxorubicin (page 92, 2nd column, 2nd paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the coupled antibody as taught by Saragovi et al. to include a cleavable linker between the antibody and cytotoxic antibody in view of the teachings of Webb et al. One would have been motivated to do so because Webb et al. teach that the incorporation of a cleavable linker between the binding agent and moiety enables the moiety to be released once absorbed by the nerve cell, e.g., TrKA receptor. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the coupled antibody as taught by Saragovi et al. to include a cleavable linker between the antibody and cytotoxic antibody in view of the teachings of Webb et al., one would achieve a method of treating a tumor, wherein the cytotoxic agent is released from 5C3 within the tumor.

Moreover, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the coupled antibody as taught by Saragovi et al. to include doxorubicin as the cytotoxic moiety in view of the teachings of Shih et al.. One would have been motivated to do so because Shih et al. teach the major limitation of conventional cancer chemotherapy is the non-selectivity of this treatment, wherein a doxorubicin immunoconjugate exhibited substantially increased tumorcidal effects over those of the unconjugated doxorubicin in the tumor system. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the coupled antibody as taught by Saragovi et al. to include doxorubicin as the cytotoxic moiety in view of the teachings of Shih et al., one would achieve a method of reducing the major limitation of non-selectivity of doxorubicin treatment.

In response to this rejection, Applicants contend that none of the cited references teach or suggest, alone or in combination, the instantly claimed invention of a method of bypassing the p-glycoprotein pump in drug-resistant tumor cells mediated by p-glycoprotein pump, in a patient having a tumor comprising tumor cells. In particular, Applicants contend that this current amendment to incorporate this language overcomes the Examiner's previous statement that the claims are drawn to a mechanism by which the compounds treat tumors. Moreover, Applicants

assert that one of skill in the art would not have a reasonable expectation based on the combined teachings of the references that the conjugated compounds could be used in a method of bypassing the p-glycoprotein pump. In this regard, Applicants reiterate their previous statement that the finding that the compounds of the invention bypass the p-glycoprotein pump after binding to tumor cells and can be used in a method of bypassing the p-glycoprotein pump as claimed herein, was unexpected. In support of this, Applicants submit a Declaration by the inventor, Dr. Uri Saragovi which supports Applicants claim that the method of bypassing the p-glycoprotein pump claimed herein could not have been predicted and represent an unexpected finding in the art.

These arguments have been carefully considered, but are not found persuasive.

In the instant case, the majority of Applicants arguments appear to center around the current amendment which incorporates the limitation "bypassing the p-glycoprotein pump in drug-resistant tumor cells mediated by p-glycoprotein pump, in a patient having a tumor comprising tumor cells" into the preamble of the claim. Thus, while the Examiner acknowledges and does not dispute Applicants assertions that the prior art does not explicitly teach bypassing the p-glycoprotein pump in drug resistant tumor mediated by p-glycoprotein, the Examiner recognizes that "bypassing the p-glycoprotein pump" occurs in the preamble of the claim and appears to recite only the purpose of the process or mechanism of the immunoconjugate. Accordingly, the recitation "bypassing the p-glycoprotein pump in drug resistant tumor cells mediated by p-glycoprotein" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 195). In the instant case, the Examiner recognizes that the prior art combination teaches the process steps of the instant claims which encompass administering to a patient having a tumor comprising tumor cells, including drug-resistant tumor cells mediated by p-glycoprotein pump, an immunoconjugate comprising an antibody which binds to a polypeptide selected from the group consisting of p17, TrKA or IGF-1R linked via breakable linker to doxorubicin or paclitaxel. As such, bypassing the p-glycoprotein pump would necessarily flow from teachings of the prior art in since the declaration teaches that the result, e.g., bypassing the p-glycoprotein pump in tumor cells,

occurs after administration of the immunoconjugate (see point 8 of the Declaration). Similarly, in view of the Declaration as well as the "whereby" clause in claim 35, it appears that Applicants have only discovered the mechanism of action of immunoconjugates in tumor cells comprising a monoclonal antibodies which binds to a polypeptide selected from the group consisting of p17, TrKA or IGF-1R. However, the courts have held that the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979).
Therefore, NO claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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